Title

Review of publications evaluating opioid use in patients with inflammatory rheumatic disease

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Authors

Anastasiou, Christine
Yazdany, Jinoos

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Review of publications evaluating opioid use in patients with inflammatory rheumatic disease.

Christine Anastasiou, MD, MAS, **Jinoos Yazdany, MD, MPH**

Division of Rheumatology, Department of Medicine, University of California, San Francisco, CA, United States.

Abstract

Purpose of review: This article discusses publications assessing the prevalence, efficacy, and safety of opioid analgesics in patients with rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, and systemic sclerosis.

Recent findings: Recent studies show long-term opioid use is common in patients with inflammatory rheumatic disease. We did not find any studies demonstrating improved function or pain control with long-term opioid use in people with rheumatic diseases. Some data shows potential adverse effects including increased risk for fractures and opioid poisoning hospitalizations. There is evidence demonstrating an association of opioid use with mental health disorders, fibromyalgia, obesity, and disability, although causative links have not been established. Only minimal reductions in opioid use were observed after initiation of biologic disease modifying antirheumatic drugs (DMARDs). Studies have shown delayed DMARD initiation and reduced DMARD use in patients on opioids, raising concerns that these analgesics may delay care or initially mask symptoms of active disease.

Summary: Available literature highlights high levels of opioid use in people with rheumatic disease, without scientific evidence to support efficacy for chronic pain control and increasing evidence of adverse events. These findings strongly suggest that opioids do not have a routine role in the chronic management of inflammatory rheumatic diseases.

Keywords

Inflammatory arthritis; Opioid; Pain

Introduction

Patients with inflammatory rheumatic diseases are often afflicted with acute and chronic pain. Chronic non-cancer pain can be due a variety of factors including active inflammatory disease, accumulated damage from disease or treatment, injury, neurologic or neuropathic disease, central pain disorder, or other conditions [1–4]. The Centers for Disease Control and Prevention (CDC) have developed guidelines for chronic pain treatment, and appropriate opioid use in the general population [2]. Based on the CDC review of the literature through

Corresponding author: Jinoos Yazdany, Jinoos.Yazdany@UCSF.edu, Phone number: (415) 353-2497.

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2016, there was no evidence of long-term benefit of opioids for chronic non-cancer pain and function, and they recommended against routine use of opioid medications for chronic musculoskeletal pain because of concerns regarding safety and inefficacy [2].

Addressing pain in inflammatory rheumatic diseases can present unique clinical challenges but is essential. Pain relief has historically been rheumatoid arthritis (RA) patients' highest priority [5]. All practitioners treating patients with inflammatory rheumatic disease are faced with the difficult responsibility of identifying the underlying cause of each person's pain and compassionately trying to improve patient comfort with a combination of nonpharmacologic therapy and a limited number of pharmacologic options.

In this review, we examine the most recent publications evaluating opioid use in patients with inflammatory rheumatic disease, including any evidence for efficacy, associated risk factors, relation to DMARD therapy, and potential adverse effects. We divide the review article into sections evaluating opioid use in each of 5 inflammatory rheumatic diseases commonly clinically associated with pain: rheumatoid arthritis, systemic lupus erythematosus, psoriasis and psoriatic arthritis, ankylosing spondylitis, and systemic sclerosis.

Rheumatoid Arthritis

Prevalence of opioid use in RA.—Chronic opioids are prescribed to 17% to 67% of US patients with RA. The highest recent estimate is from a study of Social Security Disability Insurance beneficiaries less than 65 years of age (Table 1) [6*,7*,8*,9**,10–14]. A cross-sectional study of the National Ambulatory Medical Care Survey examining data from 2011–2016 showed that one fourth of US office visits for RA involved an opioid prescription; opioid prescribing for outpatient RA visits increased from 15% to 34% ($p<0.0001$) over the time frame; and primary care physicians were the most common prescribers [*6]. Among US rheumatologists, there is likely high variability in prescribing patterns between physicians, such that RA patients cared for by the same rheumatologist are more or less likely to be opioid users based on their physician's practice [11,15].

Efficacy and safety of opioid use in RA—There is no evidence to support the efficacy and safety of long-term opioid use for RA. The most relevant study of interest was a randomized trial examining chronic opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis [16]. This trial was conducted between 2013–2015 at Veterans Affairs primary care clinics where patients were randomized to receive opioid or non-opioid analgesics. There was no significant difference in pain-related function over 12 months, and pain intensity was significantly better in the non-opioid group with less adverse medication-related symptoms. Although the results of this study may not fully capture opioid treatment outcomes for patients with inflammatory arthritis, it is striking to note that chronic opioid therapy was associated with higher pain intensity with no improvement in pain-related function, supporting the notion that opioids should not be routinely used for chronic musculoskeletal pain.

Limited evidence exists to support treating RA pain short-term (<6 weeks) with weak opioids, with evidence of adverse effects [17–18]. Among patients with RA, opioid use

has been associated with increased risk of fracture (aHR 1.37 [95% CI 1.18–1.59] for weak opiates, aHR 1.53 [95% CI 1.24–1.88] for strong opiates) [19]. Increased fracture risk from opioids may be a result of cognitive side effects, more falls, or opioid-induced endocrinopathies [20–21] as identified in other patient populations. Recent evidence also demonstrates that hospitalizations for RA patients have a higher risk of primary diagnosis of opioid poisoning compared to the general population [22], emphasizing that the risks of adverse outcomes from opioids may be magnified in RA patients.

Factors associated with chronic opioid use in RA—Chronic opioid use in RA has been associated with fibromyalgia [6*,11], anxiety [11], antidepressant use [11,14], and smoking [8*]. However, antidepressants are sometimes used as a treatment modality for pain [23–24] which complicates the interpretation of antidepressant use in these studies. There is also evidence that RA patients with mental health conditions may be at higher risk for receiving chronic opioid therapy. A retrospective cohort of veterans with RA initiating opioids between 2001–2012 evaluated the association between mental health conditions including anxiety, depression, bipolar disease, posttraumatic stress disorder, and substance use disorder with risk of being treated with chronic opioids [25**]. Veterans with mental health conditions were at higher risk than those without mental health conditions to receive long-term opioid therapy [adjusted hazard ratio (aHR) 1.18, 95% CI 1.09, 1.29], with the risk being highest for those with a history of substance use disorder. This study emphasizes the importance of evaluating and treating comorbid mental health conditions concomitantly with patients' autoimmune disease as part of a comprehensive treatment approach.

Disability has also been associated with long-term opioid use in multiple studies [7*–8*,14]. Baker and colleagues [8*] reported results from the FORWARD databank between 1999 and 2019 showing that obese RA patients had greater comorbidities, pain, and disability. Higher BMI in this study was associated with higher risk of chronic opioid use, and severe obesity was associated with a higher risk of strong opioid use [aHR 2.1, 95% CI 1.6–2.7]. Reducing obesity rates could be one potential intervention to decrease disability, pain, and chronic opioid use among patients with RA and deserves further investigation.

Initial opioid prescription duration may also be a risk factor for chronic opioid use [26]. Liberman, et al reported that RA patients prescribed a longer initial opioid prescription duration had a higher risk of being on chronic opioids thereafter compared to patients receiving initial 0–7-day prescriptions [aHR 1.52, 95% CI 1.16–2.01 for 16–29-day prescriptions; aHR 1.78, 95% CI 1.53–2.08 for 30 day prescriptions] [25**]. Almost 60% of patients were given a 30-day supply at onset of therapy. One possible explanation is that patients receiving shorter duration prescriptions had acute pain anticipated to resolve quickly, whereas patients who received longer prescriptions were being treated for chronic pain processes. Alternatively, longer duration of initial prescriptions may increase the risk of opioid dependence.

Higher disease activity [14] or longer disease duration [8*] are also associated with opioid use which raises the question of whether these patients' RA is sufficiently treated. Administrative data from the US military TRICARE program showed that patients prescribed opioids for incident RA had greater delays until initiation of DMARD therapy

(mean 212 days) compared to patients with incident RA who did not use opioids (mean 77 days, p<0.0001 for the difference) [27]. Another study evaluating RA patients with commercial insurance plans or a Medicare Advantage Prescription Drug Plan, found that opioid use was associated with lower DMARD use [13]. These study results suggest that early opioids may improve pain in the short-term, resulting in delayed DMARD therapy or lower DMARD use. Furthermore, different studies have shown that opioid use only modestly decreased after initiation of biologic therapies (Table 2). The most recent publication on this topic found that although opioid use significantly decreased 12 months after RA patients initiated biologic medications, the overall prevalence of opioid use remained high at 40% [9**]. It is unknown whether these patients use opioids after biologic initiation because of persistent inflammatory disease activity not sufficiently controlled on therapy, persistent pain not due to active RA, patient reluctance to stop opioids, or lack of physician initiative to taper opioids after initiating biologic therapy.

Systemic Lupus Erythematosus

Prevalence of opioid use in SLE (Table 1)—Patients with SLE are more likely to receive long-term opioid prescriptions compared to patients without rheumatic disease [28–29]. Retrospective analysis from the Truven MarketScan® administrative claims database from 2012–2018 showed that 53% of SLE patients used opioids in one year, with 18% chronic use [30*]. There was no difference in the prevalence of opioid use in the 6 months prior to compared to the 6 months after initiation of belimumab, despite a decrease in oral corticosteroids after belimumab [30*]. The underlying reason for persistent opioid use after therapy was not identified.

Efficacy and safety of opioid use in SLE—There is no evidence to support chronic opioid therapy in SLE, and increased opioid utilization may lead to worse outcomes for SLE patients. In 2016, US hospitalizations for SLE patients had over a 2-fold higher estimated risk of a primary diagnosis of opioid overdose compared to other hospitalizations [22].

Factors associated with chronic opioid use in SLE—Focusing on SLE ED encounters may help identify risk for and prevent some chronic opioid use in SLE patients. SLE patients using opioids were more likely to have had an emergency department (ED) visit within the preceding 12 months [28]. Lee and colleagues evaluated SLE patients with frequent ED visits at one tertiary academic medical center [31–32*]. They found that one third of these patients were on long-term opioid therapy, 55% had pain related diagnoses on ED discharge, opioids were administered during 38% of encounters, and 17% of the ED discharges included an opioid prescription. Future research can identify potential outpatient and ED interventions to reduce visits for chronic pain, and to prevent long-term continuation of opioids started for acute pain.

Psoriasis and Psoriatic Arthritis

Pain in psoriasis and psoriatic arthritis—Psoriatic arthritis is diagnosed in a fourth of patients with psoriasis and can cause painful arthritis or enthesitis [33]. Psoriatic skin lesions can also be painful [34*]. Approximately half of patients with psoriasis and without diagnosed psoriatic arthritis report moderate to severe joint pain, a greater proportion than

controls [34*], which could potentially indicate underdiagnosed and undertreated psoriatic arthritis, or noninflammatory processes which are causing joint pain in this population.

Prevalence of opioid use in psoriasis or psoriatic arthritis (Table 1)—A recent study from the Danish Skin Cohort reported that patients with psoriasis and psoriatic arthritis are more likely to use opioids than the general population (18–25% of patients with psoriatic arthritis, 13–15% of patients with psoriasis, and 9% of control patients used an opioid within a year) [34*]. Furthermore, the rate of outpatient opioid prescribing for patients with psoriasis or psoriatic arthritis has increased over time in the US from an estimated 4.9% of outpatient visits in 2006–2011 up to 16.3% of outpatient visits in 2012–2016 [35].

Patients prescribed biologic therapy also have a high rate of opioid use. Psoriatic arthritis patients taking a TNFi or anti-interleukin (IL)-12/23 inhibitor have frequently (17%) been prescribed opioid medications [36]. Moreover, Hunter and colleagues showed that opioid use only decreased a small amount (38.1% versus 33.8%, p=0.013) after biologic initiation in an analysis of 2013–2019 claims data [9**].

Factors associated with opioid use in psoriasis or psoriatic arthritis—As noted in other rheumatic diseases, depression and anxiety are common comorbidities for patients with psoriasis or psoriatic arthritis [36–37]. Depression may be associated with opioid prescription among patients with psoriasis [38].

Ankylosing Spondylitis

Prevalence of opioid use in AS—Ankylosing spondylitis is a chronic inflammatory disease affecting the axial spine and commonly associated with stiffness and pain. Few publications evaluate opioid use in patients with AS. Despite a lack of evidence, opioid use is common among patients with AS with an estimated prevalence of 19%–57% (Table 1) [39–41]. In a recent retrospective analysis, opioid use only slightly decreased without statistical significance in the 12 months after biologic initiation (42.6 vs. 36.2%, not significant) [9**].

Factors associated with opioid use in AS—An increased association between chronic opioid use and anxiolytic or muscle relaxant use has been described in different AS cohorts [40–41]. These medication combinations could potentially raise the risk for oversedation.

Systemic Sclerosis

Our literature search did not identify relevant recent publications examining the efficacy, tolerability, or side effects of oral opioids among patients with systemic sclerosis. There is sparse prior literature in systemic sclerosis discussing the efficacy of opioid analgesics to manage painful skin ulcers [42–43]. Since these patients often experience pain from inflammatory arthritis and other disease manifestations, we suspect a large proportion of patients with scleroderma may be receiving chronic opioids.

Discussion

Although there is no available data showing benefit of long-term opioid use in patients with inflammatory rheumatic diseases, there is a high rate of opioid use in these patients, and high persistent use even after initiating biologic therapy. Chronic opioid therapy for non-cancer noninflammatory musculoskeletal pain has been associated with increased pain intensity and no improvement in pain related function long-term [16]. Chronic opioids can also cause nausea, altered mental status, dependence, addiction, and opioid induced hyperalgesia [44–46]. Available evidence suggests potential adverse effects of opioids in patients with rheumatic disease, including increased fracture risk, increased opioid overdose hospitalizations, and delayed or diminished use of appropriate DMARD therapy.

Nevertheless, in select patients the benefits of chronic opioid therapy may outweigh the risks. Randomized controlled trials or observational studies evaluating the efficacy of chronic opioid therapy, specific indications, and the full spectrum of potential adverse effects in patients with inflammatory rheumatic disease is lacking and warrants further exploration.

Expert committee recommendations provide some guidance regarding pain control for certain rheumatic conditions. The European League Against Rheumatism (EULAR) [47] recommendations for pain control for inflammatory arthritis and osteoarthritis focus on a patient centered approach, with treatment including a combination of education, orthotics, psychosocial interventions, sleep hygiene education, physical activity, weight management, and pharmacological therapies first considering paracetamol and intra-articular injections as well as treating active inflammation with DMARDs to prevent damage accumulation. The guidelines from the Assessments in Spondyloarthritis International Society (ASAS)/EULAR notes a lack of formal evidence for opioids in AS and makes a weak recommendation by expert opinion to consider opioid medications for residual pain if recommended treatments for AS have failed or were poorly tolerated [48]. Given the high prevalence of chronic pain among patients with rheumatic disease, future task forces in rheumatology may consider investigating and providing additional formal guidance regarding appropriate pain management and opioid use.

Prior to initiating opioids in patients with inflammatory rheumatic conditions, treating practitioners may consider the origin of a patient’s pain to treat the underlying disease process appropriately (eg. undertreated active inflammatory arthritis, irreversible joint damage, fibromyalgia or other pain syndrome, etc.) preserving opioids for severe acute pain, and aiming to minimize routine long-term use. Moreover, the therapeutic objective of treatment, whether improved function or quality of life or other reason needs to be determined prior to initiation, and with the understanding that there is currently no evidence showing improved function or pain in patients with inflammatory rheumatic diseases on long-term opioids.

Resources are available to help patients and providers who jointly thoughtfully decide to initiate opioid tapering. Taper may not be appropriate for all patients. Reducing opioid use is not an authoritative process, but instead individualized through shared decision-making and based on patient goals and comorbidities. Although short-term pain often increases

during taper, tapering opioids may be associated with improved function, sleep, mood, and either unchanged or reduced pain long-term for many patients [49–52]. The figure (Figure) provides a summary of selected steps in opioid tapering [2,49,50] and additional resources can be obtained from the CDC [2,49]. Opioid tapering has inherent risks (withdrawal symptoms, worsened pain, patient opioid seeking behaviors either within or outside the healthcare system, overdose with reinitiation of prior high doses), and often requires a pain specialist and multidisciplinary involvement to improve patient outcomes.

Conclusion

Future research should evaluate whether chronic opioids have efficacy, even for narrow indications, in patients with inflammatory rheumatic disease and should identify alternative nonpharmacological and pharmacological tools for pain management in rheumatic diseases with a goal to reduce initial opioid prescriptions for non-acute pain.

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Key points:

- Chronic opioids are commonly prescribed for patients with RA, SLE, psoriasis or psoriatic arthritis, and ankylosing spondylitis, with evidence of associated adverse effects.
- Opioid use minimally decreased but remained high after biologic DMARD medications were initiated.
- There is no data reporting improved function, quality of life, or pain control with long-term use of opioids for patients with inflammatory rheumatic diseases, making this an important area for future research.

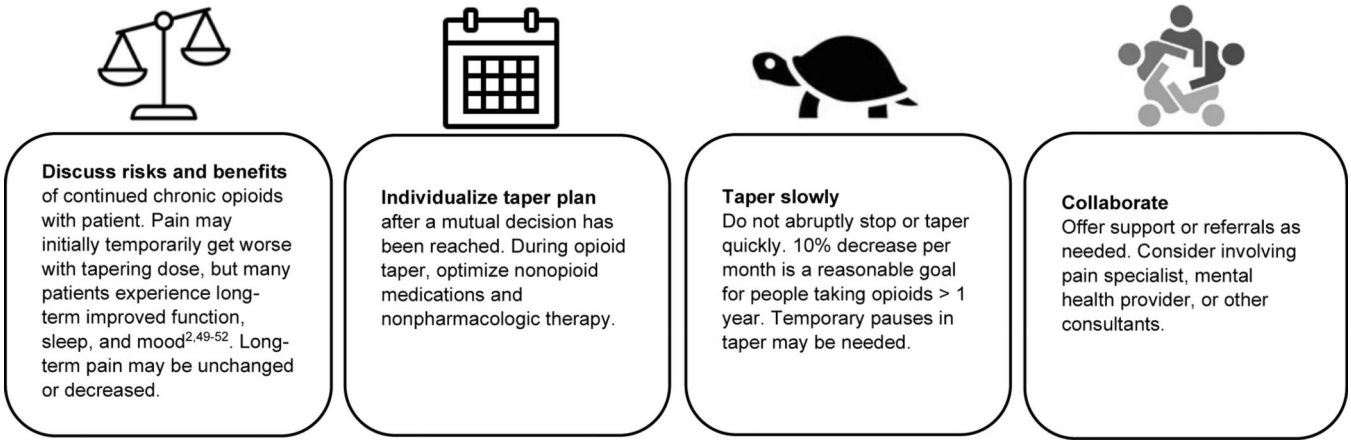

Figure.
Steps for opioid tapering.

Table 1.

Selected studies reporting opioid use among patients with rheumatic diseases (original)

Reference	Data Source	Study design	Patients	Summary of Opioid use
Rheumatoid Arthritis (RA)				
Baker, et al. [8*]	FORWARD databank	Cohort study, 1/1999–2/2019	37,868 patients with RA	27% Any opioid use
Chen, et al. [29]	Truven Health MarketScan® claims data	Retrospective observational study of US claims data, 2003–2014	181,710 patients with RA	19% Chronic opioid use
Curtis, et al. [11]	US Medicare data	Retrospective observational study of US Medicare data, 2006–2014	240,750 patients with RA	41% Chronic opioid use, 19% Intermittent opioid use in 2014.
Huang, et al. [6*]	National Ambulatory Medical Care Survey, 2011–2016	Cross-sectional survey, 2011–2016	Estimated 4.5 million encounters with primary diagnosis of RA	Proportion of visits with opioid prescription: 24.3%
Lee YC, et al. [14]	Corrona RA registry	Cohort study, 2002–2016	33,739 patients with RA	16.9% Chronic^{+} opioid use in 2015
Navarro-Millán, et al. [7*]	Medicare and Medicaid services claims data	Retrospective observational study of US claims data, 2007, 2011, 2014	43,563 patients with RA < 65 years old receiving SSDI Medicare and Medicaid	63.7% Chronic opioid use in 2014
Park, et al. [10]	IQVIA™ Health Plan Claims Data	Retrospective observational study of US claims data, 2007–2015	2,330 patients with RA	51.0% Any opioid use
Systemic Lupus Erythematosus (SLE)				
Birt, et al. [30*]	IBM® MarketScan® Databases	Retrospective observational study of US claims data, 1/2012–5/2018	49,413 patients with SLE	52.6% Any opioid use 34.6% Chronic opioid use
Chen, et al. [29]	Truven Health MarketScan® claims data	Retrospective observational study of US claims data, 2003–2014	45,834 patients with SLE	16% Chronic opioid use
Lee J, et al. [32*]	Single institution chart review	Retrospective observational chart review, 2013–2016	77 SLE patients who had persistent frequent ED visits	37.7% Chronic opioid use
Somers, et al. [28]	MILES Cohort	Prospective cohort, 2/2014–9/2015	462 SLE patients	31.0% Any opioid use 21% Chronic^{++} opioid use
Psoriasis and Psoriatic Arthritis (PsA)				
Chen, et al. [29]	Truven Health MarketScan® claims data	Retrospective observational study of US claims data, 2003–2014	30,307 patients with PsA	15% Chronic opioid use
Hunter, et al. [9**]	HealthCore Integrated Research Database®	Retrospective observational study of US claims data, 1/2013–7/2019	921 patients with psoriatic arthritis	33.8% Any opioid use 12 months after initiation of biologic
Loft, et al. [34*]	Danish Skin Cohort	Prospective cohort study	4016 patients with psoriasis, 847 with concomitant PsA.	13%–25.6% Any opioid use within the past year
Noe, et al. [38]	Optum Electronic Health Records Database	Retrospective study of US claims data, 1/2007 – 6/2017	99,830 patients with psoriasis.	1.9% of opioid-naïve patients with psoriasis received an incident opioid prescription over one year.
Taylor, et al. [35]	National Ambulatory Medical Care Survey (2006–2016) & National Hospital Ambulatory Medical Care Survey (2006–2011)	Cross-sectional survey, 2006–2016	1148 encounters for psoriasis and PsA evaluated, weighted to a US national estimate of 27 million visits	Proportion of visits with opioid prescription: 10%

Reference	Data Source	Study design	Patients	Summary of Opioid use
Walsh, et al. [36]	Optum Research Database	Retrospective study of US claims data, 1/2012 – 4/2016	1,235 patients with PsA	48.6% Any opioid use
Ankylosing Spondylitis (AS)				
Chen, et al. [29]	Truven Health MarketScan® claims data	Retrospective observational study of US claims data, 2003–2014	7,686 patients with AS	25% Chronic opioid use
Dau, et al. [40]	Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS)	Prospective cohort study	706 patients with AS	31.2% Any opioid use 9.5% Chronic^{+++} opioid use
Hunter, et al. [9**]	HealthCore Integrated Research Database®	Retrospective observational study of US claims data, 1/2013–7/2019	188 patients with AS	36.2% Any opioid use after initiation of biologic
Hwang, et al. [39]	PSOAS	Prospective cohort, 2003–2017	991 patients with AS	19.0% Any opioid use
Sloan, et al. [41]	Truven Health MarketScan® claims data	Retrospective observational study of US claims data, 1/2012–3/2017	12,862 patients with AS (ICD 720.0).	Commercial claims: 23.5% Chronic opioid use Medicaid claims: 57.1% Chronic opioid use

Unless otherwise specified, chronic opioid use can be summarized as ≥ 90 days of opioid prescription or opioid use.

Chronic +: opioid use at ≥ 2 consecutive study visits which are ≥ 3 months apart. Chronic ++: Opioid use for ≥ 1 year. Chronic +++: Daily opioid usage > 6 months. Legend. MILES: Michigan Lupus Epidemiology and Surveillance Program.

Table 2.

Changes in opioid use after starting biologic therapy for rheumatoid arthritis (original).

Reference	Population	Time frame	Major results
Accortt, et al. [12]	Truven Health MarketScan® claims data	2010 – 2013	Opioid use (y/n) modestly decreased from 54.8% to 52.2% within the 12 months after initiation of etanercept ($p < 0.001$).
Hunter, et al. [9**]	HealthCore Integrated Research Database® claims data	2014 – 2017	Opioid use (y/n) decreased 12 months after initiating biologic therapy in patients with rheumatoid arthritis (52.0 versus 40.4%, $p<0.001$).
Park, et al. [10]	IQVIA™ Health Plan Claims Data	2007 – 2015	Opioid use (y/n) modestly decreased from 54.0% to 51.0% ($p = 0.006$) after initiation of TNFi. 38.8% used chronic opioids over entire 24-month study. Twenty-eight percent of patients who had opioid use prior to TNFi initiation discontinued opioids thereafter, but 26.5% not prescribed opioids prior to TNFi initiated opioids after TNFi was started. The proportion of patients receiving ≥ 50 mg median daily morphine equivalent dose modestly decreased from 12.6% to 10.6% in the 12 months after TNFi initiation ($p = 0.005$).

Legend. TNFi = tumor necrosis factor inhibitor. y/n: Yes/No.